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Expression in cytotoxic T lymphocytes of a single-chain anti-carcinoembryonic antigen antibody. Redirected Fas ligand-mediated lysis of colon carcinoma.

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In the MD45 mouse cytotoxic T lymphocyte (CTL) hybridoma cell line, we have expressed a chimeric receptor, consisting of the single-chain variable domains (scFv) of anti-carcinoma embryonic antigen (CEA) mAb linked to Fcgamma receptor (FcgammaR) chain via a CD8 hinge. Transfected MD45 subclones lysed CEA-positive human colon carcinoma cell lines in an antigen-specific and FasL-dependent manner. The degree of lysis correlated with the level of chimeric receptor expressed on transduced MD45 subclones. The requirement for an intact Y65TGL motif in the signaling gamma chain suggested that interaction of the chimeric receptor with target cell CEA induced the cytotoxicity of MD45-scFv subclones. However, MD45 expressing a Y65F mutant chimera still displayed minor levels of lysis following PMA stimulation, suggesting that PMA could bypass gamma chain induction of functional FasL. Pretreatment of Fas-resistant CEA-positive colon carcinoma target cells with IFN-gamma increased their sensitivity of MD45-scFv subclones and FasL-mediated lysis. This study has demonstrated the successful activation of FasL function via a chimeric receptor introduced into lymphocytes and the susceptibility of human colon carcinoma to combined cytokine and CTL treatment.